Article abstract—Choline acetyltransferase (ChAT) activity was studied in different areas and in sequential sections of the cortical layers in the first temporal gyrus of left and right hemispheres of four human brains. The ChAT activity values obtained in all the samples from left hemisphere were significantly higher than in the right hemisphere. Furthermore, the study of ChAT activity in the cortical layers in Brodmann area 22 shows a greater left prevalence of enzymatic activity in cortical layers II and IV. The biochemical data seem to suggest a possible morphologic and/or functional difference between the two hemispheres.

NEUROLOGY (Ny) 1981;31:799-805

Choline acetyltransferase (ChAT) activity differs in right and left human temporal lobes

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Several higher cortical functions (such as language, visual-spatial analysis, and memory) are represented asymmetrically in the right or left hemisphere. Anatomic asymmetry has also been described[1,2]; in particular, the sylvian fissure and its posterior part (the planum temporale) are longer on the left in most adult brains. However, little is known about possible neurochemical correlates of hemispheric specialization; only one report[3] has provided evidence of significant lateralization of a neurotransmitter (norepinephrine) in human thalamus. In a study[4] of choline acetyltransferase (ChAT; EC 2.3.1.6) enzyme activity in Alzheimer-disease brains varied from control brains, and hemispheric differences were considered.

Because the cholinergic system seems to be involved in memory and cognitive functions,[5,6] we thought it important to compare ChAT activity in the right and left first temporal gyrus, which shows a marked lateral asymmetry from the functional point of view (Wernicke area). Preliminary data[7] indicated that ChAT activity was higher in the first temporal gyrus on the left. This observation stimulated a more extensive study. Because of limitation of available tissue, the most pertinent components to be measured, besides total protein, were galactolipids (cerebrosides and sulfatides), because the distribution of galactolipids is correlated with myelinated nerve fibers[8] and because the number of cortical neurons is similar in different areas but the number of connecting fibers differs.[9-11] Moreover, variations in ChAT activity have been correlated with functional/morphologic changes in the fiber pathways leading to the cortex.[12-14]

Materials and methods. *Autopsy material.* ChAT activity can be measured in postmortem brains; the decline of enzyme activity is slow and linear.[15-16] We studied four brains of patients who died with no classical or pathologic signs of neurologic disease. Those four men all died suddenly (table 1) and the brains were frozen at -50° C for no more than 2 weeks.

Sampling methods. The intersection of a hypothetical line connecting the fissures of Sylvius and Rolando was taken as a point of reference. Specimens of the first temporal gyrus were collected with a hollow punch of 1.4 mm internal diameter. The length of the tissue cylinder was 2 mm and the average (± SD) fresh weight of the tissue was 2.87 ± 0.12 mg. The first specimen was taken 1 cm rostral to the reference point, and the following samples (punches 2, 3, 4, 5, 6) were obtained at distances of 1 cm in the rostrocaudal direction (figure 1), 0.5 cm below the sylvian fissure.

To study the cortical layers, we used the technique of Linderstrom-Lang and Mogensen[17] as

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This study was supported by Grant No. 79.01817 from C.N.R. (Rome, Italy).

Accepted for publication December 3, 1980.

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Reprinted from NEUROLOGY, Vol. 31, No. 7, pp. 799-805, July 1981

modified by Pope et al.[18] Specimens were collected with a hollow punch of 3.3 mm of internal diameter. Tissue cylinders were collected at the line of punch number 4 (which previously showed the greatest differences) 0.5 cm below the previous punched area and corresponding to Brodmann area.[19-22] The frozen cylinders were cut into sequential sections 50 μ thick, with a volume of 0.427 mm^3, using a cryomicrotome LKB 2250. The frozen slices were dried in a desiccator for 24 hours.

Biochemical methods. Choline acetyltransferase assay. ChAT was assayed by the micromethod of Fonnum[20] measuring the conversion of labeled acetyl-CoA into labeled acetylcholine (Ach). Tissue was homogenized with 10 mM EDTA (sodium salt; 1/20 w/v), and the homogenate treated with 0.3% final concentration of Triton X-100. Aliquots (2 μl) of the homogenate were added to 5 μl of incubation medium and incubated for 30 minutes at 37° C in a Dubnoff shaker. The composition of the incubation medium, expressed in mM as final concentration, was as follows: $1^{-14}C$ acetyl-CoA (specific activity 59 mCi per millimole, obtained from the Radiochemical Centre, Amersham) 0.2; EDTA salt (pH 7.4) 10; choline chloride 10; NaCl 300; sodium phosphate buffer (pH 7.4) 41; physostigmine salicylate 0.1; and Triton X-100, 0.05%. The labeled acetyl-CoA was diluted with unlabeled compound (Biochemia Boehringer) to give, finally, 16.9 mCi per millimole.

After incubation the reaction tubes were transferred directly to scintillation vials. The contents of the tubes were washed out with 5 ml of 10 mM sodium phosphate buffer and the ^{14}C-ACh was extracted directly into 10 ml of toluene scintillation mixture plus 2 ml acetonitrile containing 10 mg of tetraphenylboron (Kalignost). When the two layers were separated, ^{14}C was counted in a Beckman LS 100 liquid scintillation counter with a counting efficiency of 85% calculated by the external standard method.

Estimation of cerebrosides. The general scheme of analysis, as well as the procedures for lipid extraction and partition, were carried out by a microversion of the technique of Folch et al[21] as modified by Hess and Thalheimer.[22] For determination of neutral cerebrosides and sulfatides, the orcinol-sulfuric acid reaction[23,24] adapted to the microscale by Hess and Lewin[26] was used. The intracortical

Table 1. Autopsy material data

Case No.	Age/Sex	Hemispheric dominance	Cause of death	Time specimens collected after death (hrs)
1	55/M	Right-handed	Acute pulmonary edema	12
2	59/M	Right-handed	Cardiac tamponade	16
3	66/M	Right-handed	Myocardial infarction	16
4	89/M	Right-handed	Myocardial infarction	16

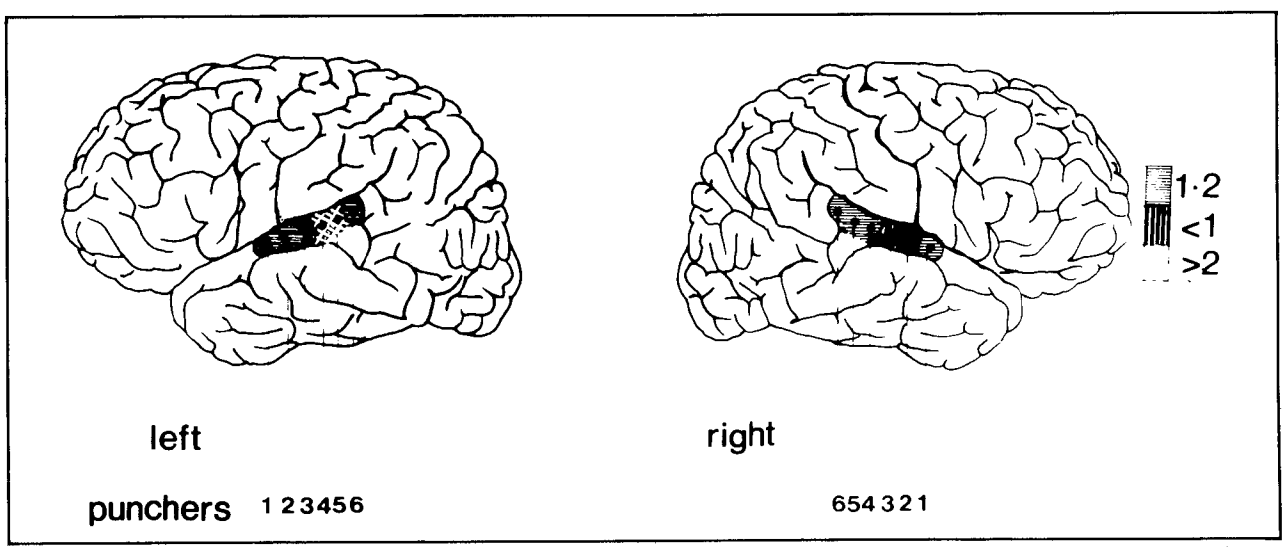

Figure 1. ChAT activity in the first temporal gyrus of left and right hemispheres. The specimens were punched at 0.5 cm below the fissure of Sylvius. The first specimen was punched out 1 cm rostrally to the intersection of a hypothetical line connecting the fissures of sylvius and Rolando, and the following samples were punched at 1 cm in the rostrocaudal direction. ChAT activity was expressed as micromoles of ACh synthesized per hour/100 mg dry weight.

Table 2. ChAT activity in the first temporal gyrus of left and right hemispheres

	ChAT (μmoles/h/100 mg dry weight)								
	Case	1	Case	2	Case	3			
	Age	55	Age	59	Age	89	Mean ± S.D.		
Punch	L	R	L	R	L	R	L	R	$p <$
1	1.92	1.22	1.44	0.75	1.18	0.76	1.51 ± 0.37	0.91 ± 0.26	0.005
2	0.92	0.47	1.29	0.59	1.04	0.58	1.08 ± 0.18	0.54 ± 0.06	0.005
3	1.66	1.27	1.60	0.52	1.52	0.50	1.59 ± 0.07	0.76 ± 0.43	0.005
4	1.94	1.00	2.11	1.30	2.28	1.47	2.11 ± 0.17	1.25 ± 0.23	0.001
5	1.32	0.82	1.94	1.45	2.27	0.90	1.84 ± 0.48	1.05 ± 0.34	0.05
6	1.18	0.84	1.07	0.75	0.96	0.87	1.07 ± 0.11	0.82 ± 0.06	0.05

The specimens were punched as in figure 1.
L = left.
R = right.

Table 3. Cerebroside concentration in the first ±temporal gyrus of left and right hemispheres

	Cerebroside as percentage of dry weight								
	Case	1	Case	2	Case	3			
	Age	55	Age	59	Age	89	Mean ± S.D.		
Punch	L	R	L	R	L	R	L	R	$p <$
1	1.30	1.27	1.33	1.30	1.30	1.37	1.31 ± 0.01	1.31 ± 0.05	N.S.
2	1.33	1.37	1.27	1.50	1.45	1.50	1.35 ± 0.09	1.45 ± 0.07	N.S.
3	1.40	1.25	1.50	1.55	1.40	1.55	1.43 ± 0.05	1.45 ± 0.17	N.S.
4	1.50	1.42	1.45	1.27	1.07	1.35	1.34 ± 0.13	1.34 ± 0.07	N.S.
5	1.45	1.46	1.27	1.17	1.27	1.17	1.33 ± 0.10	1.26 ± 0.16	N.S.
6	1.27	1.50	1.30	1.45	1.32	1.45	1.29 ± 0.02	1.46 ± 0.02	N.S.

The specimens were punched as in figure 1.
L = left.
R = right.
N.S. = Not significant.

distribution of these compounds agreed with data previously reported.[8]

Total protein determination. Total protein was measured in the portion of the homogenate used for ChAT assay by the method of Lowry[25] as modified.[26] The intracortical distribution of total protein agreed with data in the literature.[27]

Histologic controls. Assessment of deviation of tissue cylinders from an axis perpendicular to the pial surface and the plane of the cortical layers was carried out according to the methods of Pope et al.[18] Cortical layers were identified by the Nissl and myelin staining methods (Weigert) of sections cut in a direction perpendicular to the pial surface of the formalin-fixed blocks. The cortex corresponding to punch number 4 was identified as a typical six-layer cortex as described by Von Economo[28]; with these methods, we found no differences in the cytoarchitecture of left and right hemispheres.

Results. ChAT activity in all the specimens examined was always higher in samples from the left hemisphere. The greatest differences appeared at the levels of punch Number 4 (3 cm caudal to the reference point, Brodmann area 22) (table 2). There were no differences in the galactolipid concentration (table 3). In both hemispheres, there were two peaks of maximum ChAT activity corresponding to the second and fourth cortical layers (table 4, figure 2) again higher on the left. Galactolipids and total protein content, however, were similar in the two hemispheres, and close to reported values for Brodmann areas 9 and 10[8,27] (table 5, figure 3).

Discussion. Terminal bronchopneumonia, coma, or anoxia may decrease ChAT values; for this reason, we used cases of sudden death. Age may also be important in evaluating ChAT activity.[15,16] Cases 1-3 had an average age of 60 and had no signs of mental deterioration, but there was doubt about the mental status of patient 4 (age 89). He was not discarded and the case was included because ChAT values were at exactly the same level as in the other brains. Moreover, data from cases

Table 4. ChAT activity in relation to subpial depth in human left and right first temporal gyrus

		ChAT (μmoles/h/100 mg dry weight)										
		Case	1	Case	2	Case	3	Case	4			
Series	Depth	Age	55	Age	59	Age	66	Age	89	Mean ± S.D.		
No.		L	R	L	R	L	R	L	R	L	R	$p <$
1	50	0.55	0.47	0.57	0.18	0.56	0.41	0.54	0.46	0.55 ± 0.01	0.38 ± 0.13	N.S.
2	100	0.62	0.45	0.54	0.23	0.67	0.41	0.55	0.37	0.59 ± 0.06	0.36 ± 0.09	0.001
3	150	0.71	0.48	0.56	0.49	0.69	0.44	0.56	0.41	0.63 ± 0.08	0.45 ± 0.03	0.001
4	200	0.80	0.37	0.56	0.40	0.66	0.43	0.53	0.60	0.63 ± 0.12	0.40 ± 0.02	0.01
6	300	1.39	1.02	1.60	0.27	1.40	0.93	1.29	0.97	1.42 ± 0.12	0.79 ± 0.35	N.S.
7	350	1.33	0.93	1.54	0.96	1.60	0.86	1.53	0.94	1.50 ± 0.11	0.92 ± 0.04	0.001
8	400	1.40	1.23	1.56	1.15	1.78	1.10	1.53	1.09	1.56 ± 0.15	1.14 ± 0.06	0.005
9	450	1.36	1.04	1.42	1.25	1.37	1.10	1.38	1.12	1.38 ± 0.02	1.12 ± 0.08	0.001
11	550	1.37	1.14	1.45	1.00	1.31	0.96	1.39	1.13	1.38 ± 0.05	1.05 ± 0.09	0.001
12	600	1.43	1.59	1.26	0.95	1.28	0.74	1.29	0.96	1.29 ± 0.36	1.06 ± 0.36	N.S.
13	650	1.20	0.85	1.21	0.78	1.28	0.88	1.16	0.76	1.21 ± 0.04	0.81 ± 0.05	0.001
14	700	1.28	0.83	1.14	0.79	1.39	0.63	1.13	0.67	1.23 ± 0.12	0.73 ± 0.09	0.001
16	800	1.00	0.60	0.79	0.79	0.71	0.59	0.83	0.69	0.83 ± 0.12	0.66 ± 0.09	N.S.
17	850	0.55	0.52	0.57	0.45	0.76	0.47	0.68	0.65	0.64 ± 0.09	0.52 ± 0.08	N.S.
18	900	0.58	0.50	0.75	0.52	0.72	0.67	0.57	0.59	0.65 ± 0.09	0.57 ± 0.07	N.S.
19	950	0.70	0.68	0.67	0.74	0.74	0.56	0.66	0.61	0.69 ± 0.03	0.59 ± 0.16	N.S.
21	1050	0.62	0.59	0.64	0.73	0.71	0.48	0.63	0.52	0.65 ± 0.04	0.58 ± 0.10	N.S.
22	1100	0.55	0.48	0.48	0.59	0.54	0.44	0.61	0.69	0.54 ± 0.05	0.50 ± 0.06	N.S.
23	1150	0.50	0.47	0.48	0.53	0.70	0.48	0.67	0.43	0.58 ± 0.11	0.46 ± 0.04	N.S.
24	1200	0.62	0.44	0.53	0.45	0.65	0.54	0.65	0.51	0.61 ± 0.05	0.48 ± 0.04	0.001
26	1300	0.61	0.48	0.60	0.34	0.60	0.46	0.75	0.43	0.66 ± 0.07	0.42 ± 0.06	0.001
27	1350	1.38	0.86	0.70	0.73	0.78	0.50	0.90	0.68	0.94 ± 0.30	0.69 ± 0.14	0.005
28	1400	1.00	0.82	1.12	0.70	0.74	0.53	1	0.73	0.96 ± 0.16	0.69 ± 0.12	0.001
29	1450	1.21	1.03	1.31	0.78	1.11	0.87	1.12	0.92	1.18 ± 0.09	0.90 ± 0.10	0.005
31	1550	1.24	1.22	1.62	0.99	1.34	0.97	1.43	1.18	1.35 ± 0.08	0.94 ± 0.39	0.005
32	1600	1.38	1.21	1.63	1.05	1.56	1.23	1.41	1.14	1.49 ± 0.11	1.15 ± 0.08	0.001
33	1650	1.36	1.46	1.63	1.07	1.45	1.00	1.39	1.08	1.45 ± 0.12	1.15 ± 0.20	0.005
34	1700	1.37	1.29	1.61	1.29	1.41	1.19	1.35	1.26	1.45 ±0.15	1.25 ± 0.04	0.005
36	1800	1.38	1.44	1.65	0.99	1.31	1.22	1.48	1.19	1.45 ± 0.14	1.21 ± 0.18	0.005
37	1850	1.27	1.42	1.48	1.14	1.37	0.91	1.19	1.29	1.32 ± 0.12	1.19 ± 0.21	N.S.
38	1900	1.34	1.12	1.36	1.13	1.45	1.08	1.43	1.18	1.39 ± 0.05	1.12 ± 0.04	0.001
39	1950	1.13	1.20	1.22	0.89	1.28	0.42	1.29	1.07	1.23 ± 0.05	1.84 ± 0.34	0.005
41	2050	0.69	0.59	0.78	0.51	0.68	0.43	0.70	0.68	0.71 ± 0.04	0.55 ± 0.10	N.S.
42	2100	0.61	0.55	0.76	0.54	0.79	0.42	0.84	0.57	0.75 ± 0.09	0.52 ± 0.06	N.S.
43	2150	0.62	0.44	0.63	0.48	0.75	0.42	0.59	0.68	0.64 ± 0.07	0.50 ± 0.11	N.S.
44	2200	0.48	0.39	0.58	0.37	0.64	0.33	0.55	0.49	0.56 ± 0.06	0.39 ± 0.06	N.S.
46	2300	0.47	0.35	0.52	0.36	0.36	0.33	0.46	0.42	0.45 ± 0.06	0.36 ± 0.03	N.S.
47	2350	0.37	0.33	0.32	0.31	0.46	0.31	0.38	0.32	0.38 ± 0.05	0.31 ± 0.01	N.S.
48	2400	0.34	0.40	0.37	0.40	0.40	0.43	0.36	0.45	0.36 ± 0.02	0.42 ± 0.02	N.S.
49	2450	0.25	0.64	0.35	0.37	0.33	0.43	0.27	0.39	0.30 ± 0.04	0.45 ± 0.12	N.S.
51	2550	0.31	0.33	0.28	0.29	0.34	0.36	0.27	0.42	0.30 ± 0.03	0.35 ± 0.15	N.S.
52	2600	0.25	0.30	0.27	0.29	0.33	0.30	0.27	0.38	0.28 ± 0.03	0.31 ± 0.04	N.S.
53	2650	0.15	0.23	0.20	0.22	0.21	0.22	0.21	0.25	0.19 ± 0.02	0.23 ± 0.04	N.S.
54	2700	0.16	0.23	0.19	0.23	0.22	0.22	0.18	0.32	0.18 ± 0.02	0.25 ± 0.04	N.S.
56	2800	0.17	0.15	0.20	0.17	0.21	0.19	0.17	0.26	0.18 ± 0.02	0.19 ± 0.04	N.S.
57	2850	0.15	0.20	0.17	0.16	0.20	0.18	0.15	0.27	0.16 ± 0.02	0.20 ± 0.04	N.S.
58	2900	0.12	0.18	0.16	0.18	0.16	0.18	0.15	0.24	0.14 ± 0.01	0.19 ± 0.03	N.S.
59	2950	0.10	0.21	0.15	0.17	0.14	0.19	0.13	0.22	0.13 ± 0.02	0.19 ± 0.02	N.S.

The specimens were punched as in figure 1.
L = left.
R = right.
N.S.= Not significant.

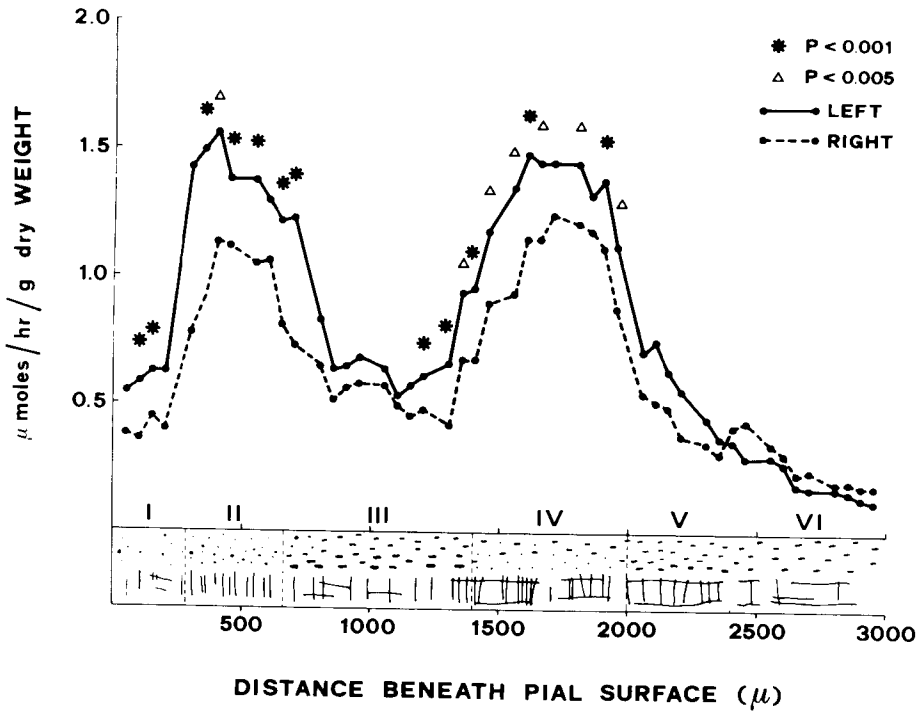

Figure 2. Intralaminar distribution of ChAT activity in cortical sequential sections of the Brodmann area 22 in the first temporal gyrus of left and right hemispheres. The specimens of four temporal lobes were collected at the line of punch 4 (see figure 1). The punches were cut into frozen sequential sections of 50 μ. Descriptions of cortical layers are according to V. Economo.[28]

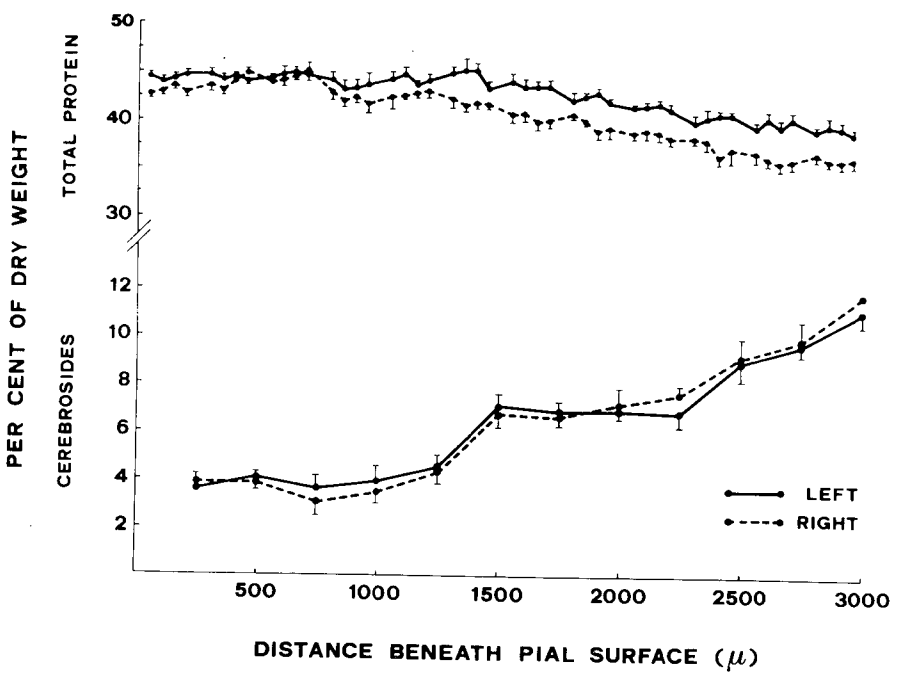

Figure 3. Intralaminar distribution of cerebrosides and total proteins in cortical sequential sections of the Brodmann area 22 in the first temporal gyrus of left and right hemispheres.

1, 2, and 3 alone showed highly significant differences between left and right hemispheres.

The average ChAT activity in an earlier study of the same areas in five "control" brains was 1.42 ± 0.14 μmol/hr/100 mg protein[14,16] and the average in the present study of all ChAT values obtained from all zones punched in the first temporal gyrus was 1.53 ± 0.38 μmol/hr/100 mg protein. It therefore seems reasonable to consider the present values as "normal." The possibility that all brains might have had a specific lesion on one side appears unlikely, considering the good agree-

Table 5. Cerebroside concentration in relation to ± subpial depth in human left and right first temporal gyrus

Series No.	Depth	Case 1 Age 55 L	Case 1 Age 55 R	Case 2 Age 59 L	Case 2 Age 59 R	Case 3 Age 66 L	Case 3 Age 66 R	Case 4 Age 89 L	Case 4 Age 89 R	Mean ± S.D. L	Mean ± S.D. R	$p <$
		Cerebroside as percentage of dry weight										
5	250	3.4	3.8	3.9	4.0	3.8	4.0	3.4	3.8	3.65 ± 0.11	3.91 ± 0.26	N.S.
10	500	4.0	3.8	4.0	4.2	4.2	4.0	3.8	3.6	4.03 ± 0.16	3.91 ± 0.25	N.S.
15	750	4.0	4.1	3.8	2.9	3.9	2.8	3.0	2.6	3.67 ± 0.45	3.12 ± 0.67	N.S.
20	1000	4.5	4.0	4.1	3.3	4.3	4.0	3.0	2.9	3.97 ± 0.67	3.54 ± 0.54	N.S.
25	1250	4.8	3.8	4.3	4.2	4.8	5.0	3.9	4.5	4.45 ± 0.43	4.37 ± 0.50	N.S.
30	1500	6.6	7.2	7.8	7.4	7.2	6.8	6.8	6.0	7.10 ± 0.52	6.85 ± 0.61	N.S.
35	1750	7.2	6.8	6.9	6.8	6.8	7.0	6.4	6.4	6.82 ± 0.33	6.75 ± 0.25	N.S.
40	2000	6.4	7.4	7.2	7.8	7.4	7.4	7.0	6.0	7.00 ± 0.43	7.15 ± 0.78	N.S.
45	2250	6.0	8.0	7.9	8.0	7.0	7.2	6.5	7.2	6.85 ± 0.81	7.60 ± 0.46	N.S.
50	2500	9.4	10.2	10.2	9.5	8.8	9.4	7.9	7.8	9.07 ± 0.97	9.22 ± 1.01	N.S.
55	2750	10.2	11.0	10.0	10.0	9.1	9.8	10.0	8.9	9.82 ± 0.49	9.92 ± 0.86	N.S.
60	3000	12.0	11.2	11.1	12.0	10.1	11.0	11.2	11.4	11.10 ± 0.77	11.40 ± 0.43	N.S.

The specimens were punched as in figure 1.
L = left.
R = right.
N.S. = Not significant.

ment of all the values and the absence of morphologic changes in the areas sampled.

The observed differences in ChAT activity therefore seem significant, implying morphologic or functional differences. However, no attempt has been made to relate these results to recognized morphologic differences between the hemispheres,[1,2] which are greater in caudal regions (planum temporale).

The data on the intralaminar distribution of ChAT confirm the previous observations[7] on larger specimens. The major differences seem to occur in cortical layers II and IV, which contain the highest number of nerve endings.[29] It is necessary to take precautions in collecting specimens perpendicular to the pial surface, but errors in technique would be demonstrated histologically, and would result in greater variability of ChAT activity of different punches and tissue slices taken at the same cortical level. Such differences did not appear in our data, and cerebroside and total protein contents were also normal. Moreover, the data reported are not at variance with a recent report[30] of lack of biochemical asymmetries between human hemispheres, since the temporal lobes were not considered.

In conclusion, our data imply a relation between the metabolism of neurotransmitters (such as ACh) involved in specific higher neuronal functions, possibly related to asymmetries of the superior temporal lobes. However, it is not possible to decide whether there is a structural difference between the two types of cortex or only different functional activity. The present data, however, seem to suggest functional asymmetry.

Acknowledgment

The authors are greatly indebted to Prof. A. Pope for his assistance in discussing the data and suggestions in preparing the manuscript.

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